Erlotinib (Tarceva) for the Treatment of Non–Small-Cell Lung Cancer and Pancreatic Cancer

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ABSTRACT

Erlotinib (Tarceva) is a small-molecule, orally dosed, anticancer drug that inhibits the epidermal growth factor receptor. Randomized, controlled clinical studies have demonstrated that erlotinib significantly improved survival in patients with previously treated non–small-cell lung cancer and, in combination with chemotherapy, in patients with untreated pancreatic cancer. In this article, we describe the clinical evidence and value of erlotinib as a therapy for non–small-cell lung cancer and pancreatic cancer and discuss ongoing clinical studies to optimize its use in various settings and to identify appropriate patient populations.

INTRODUCTION

Erlotinib (Tarceva, OSI Oncology/Genentech/Roche) is an oral, once-daily anticancer tablet that inhibits the action of the epidermal growth factor receptor *(EGFR)*.[1] This transmembrane receptor is involved in cell proliferation, growth, migration, invasion, and survival, and it has been shown to be overexpressed in a wide variety of cancers.[2] Erlotinib is the only *EGFR*–tyrosine kinase inhibitor (TKI) proven to significantly prolong survival in relapsed or refractory non–small-cell lung cancer (NSCLC) as a single agent.[3] In addition, it is the first drug in a phase 3 trial to have shown a significant improvement in overall survival when it was added to chemotherapy with gemcitabine (Gemzar, Lilly) as an initial therapy for pancreatic cancer.[4]

On the basis of these survival benefits, erlotinib was approved in 2004 as a monotherapy for previously treated, locally advanced or metastatic NSCLC, and in 2005, in combination with gemcitabine for the first-line treatment of locally advanced, unresectable, or metastatic pancreatic cancer.[5] Further, the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium has recommended erlotinib either as a single agent or in combination with chemotherapy for patients with a known active *EGFR* mutation or gene amplification who have never smoked.[6]

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NON–SMALL-CELL LUNG CANCER

Approximately 219,400 cases of lung and bronchus cancer are expected to occur in the U.S. in 2009, making lung cancer the second most common cancer.[7] The majority of these cases (87%) are NSCLC. Lung cancer is the leading cause of cancer-related deaths in both men and women, with about 159,300 deaths anticipated in 2009.[7] Among the 25 most common cancers globally, the mortality-to-incidence rate ratios for lung cancer are third highest for both men and women, preceded only by pancreatic and liver cancers. For patients with localized disease, long-term survival is attainable when patients are optimally treated with surgery and chemotherapy or radiation as indicated. However, despite decades of research, the five-year survival rate for those with distant metastases is only 2.8% in the U.S.[7]

The past two decades have seen the development of targeted agents for the treatment of NSCLC, several of which target *EGFR*. Differences in NSCLC exist beyond cell histology that may guide treatment decisions. Analyses of patients with NSCLC have revealed that individual tumors differ with respect to the presence of *EGFR*-activating mutations; the number of copies of the *EGFR* gene, as assessed by fluorescence *in situ* hybridization (FISH); and the level of *EGFR* protein expression, as assessed by immunohistochemical (IHC) analysis.[8]

Importantly, associations have been made between each of these factors and clinical outcomes as well as patient characteristics. Studies have demonstrated that the presence of an *EGFR* mutation predicts for response and improved survival with *EGFR*–TKI treatment and that these mutations are more common in never-smokers, Asians, women, and those with histological features of adenocarcinoma.[8] Increased *EGFR* gene copy number and EGFR protein overexpression have also been correlated with improved response and survival with *EGFR*–TKI treatment.[8]

The NCCN Compendium recognizes the importance of these biologic markers in treatment selection for patients with advanced NSCLC and has recommended erlotinib, either as a single agent or in combination with chemotherapy, for patients with a known active *EGFR* mutation or gene amplification who have never smoked.[6] Conversely, mutations in the Kirsten rat sarcoma (*K-ras* or *KRAS*) gene, which encodes a protein in the *EGFR*-signaling pathway, confers resistance to anti-*EGFR* monoclonal antibody agents, including cetuximab (Erbitux, Bristol-Myers Squibb/Merck/ImClone) and panitumumab (Vectibix, Amgen), in colorectal cancer.[9,10] Preliminary data

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suggest that these mutations might also confer resistance to *EGFR*–TKIs in NSCLC.[11,12] Ultimately, this challenging disease will require intelligent application of novel therapies that prolong survival and improve quality of life.

Erlotinib as Single-Agent Therapy for Previously Treated Advanced Non–Small-Cell Lung Cancer

Two *EGFR*–TKIs, erlotinib and gefitinib (Iressa, AstraZeneca), were approved in the U.S. as therapy for previously treated, advanced NSCLC. However, only erlotinib has significantly improved survival in this setting.[3,13] Although gefitinib induced responses and symptom improvement in two randomized phase 2 studies (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL-1 and IDEAL-2], a confirmatory randomized, placebo-controlled phase 3 trial—Iressa Survival Evaluation in Lung Cancer (ISEL)—did not demonstrate any survival benefit for gefitinib.[13–15]

Gefitinib has been taken off the market in the U.S. Only NSCLC survivors still responding to this agent have access to it in the U.S. In other countries outside the U.S., primarily in Asia, gefitinib is an option for previously treated, advanced NSCLC.[16]

Efficacy

The efficacy and clinical benefit of erlotinib were demonstrated in a randomized, phase 3 trial (study BR.21) of 731 patients with stage IIIB-IV NSCLC (Table 1).[3] Patients who did not respond to one or two prior chemotherapy regimens were assigned to receive erlotinib 150 mg daily or placebo.

Treatment with erlotinib resulted in improved survival, progression-free survival, and response. The erlotinib arm experienced a statistically significant 30% reduction in the relative risk of death compared with those receiving placebo (hazard ratio [HR] = 0.70; $P < 0.001$). Median overall survival rates were 6.7 months with erlotinib and 4.7 months with placebo. A 45% relative improvement in one-year survival was also observed (31.2% with the study drug vs. 21.5% with placebo).[1] Furthermore, erlotinib produced a statistically significant 39% reduction in the relative risk of progression (HR = 0.61; $P < 0.001$). Median progression-free survival and overall response rates for erlotinib and placebo were 2.2 months versus 1.8 months and 8.9% versus less than 1%, respectively ($P < 0.001$).

The median duration of response in the erlotinib group was 7.9 months. An additional important measure of efficacy beyond response is the disease control rate, a composite of the rates of complete response, partial response, and stable disease, which was 45% in the erlotinib group.

The clinical benefit of erlotinib was reported in all patient subsets, including those of age, sex, performance status, and line of therapy, with notable improvement in patients with good performance status (PS 0–1).[3,17] A separate retrospective exploratory analysis, according to patient smoking history, revealed HRs of 0.42 for never-smokers and 0.87 for smokers, indicating a beneficial effect of erlotinib in both subsets but possible preferential efficacy in never-smokers.[18]

Erlotinib also reduced symptoms in patients with advanced NSCLC.[19] It prolonged the time to deterioration for the three main symptoms of lung cancer: dyspnea, cough, and pain ($P < 0.05$ for each), and it was associated with improved physical functioning in a quality-of-life analysis.

Table 1 **Clinical Efficacy of Erlotinib as Second-Line or Third-Line Therapy for Advanced Non–Small-Cell Lung Cancer**

Author/Study	Description	No.	Treatment	Efficacy
Shepherd et al., 2005[3]	Phase 3 (study BR.21)	731	Erlotinib vs. placebo	Median OS: 6.7 months vs. 4.7 months; HR = 0.70 ($P < 0.001$) 1-year survival: 31.2% vs. 21.5% Median PFS: 2.2 months vs. 1.8 months; HR = 0.61 ($P < 0.001$) ORR: 8.9% vs. <1% ($P < 0.001$); DCR with erlotinib: 45% Median survival by grade of rash (erlotinib arm) • grade 0: 3.3 months • grade 1: 7.1 months • grade 2+: 11.1 months ($P < 0.001$)
Spigel et al., 2008[25]	Phase 3b (expanded access)	229	Erlotinib	OS: 6.3 months ORR: 8.3% DCR: 31.4%
Groen et al., 2008[20]	Phase 4 (TRUST)	7,043	Erlotinib	PFS: 3.2 months ORR: 12.6% DCR: 68.8%

DCR = disease control rate (complete response + partial response + stable disease); HR = hazard ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Safety and Tolerability

Erlotinib was generally well tolerated in the BR.21 study. The most commonly occurring grade 3 or 4 toxicities were skin rash (9%), anorexia (9%), and diarrhea (6%). Including data from study BR.21, the safety profile of erlotinib has been established in more than 9,000 patients in clinical trials and expanded access programs.[3,20–22] Adverse effects, most commonly diarrhea and skin rash, were predictable, generally mild (grade 1 or 2), and manageable.

Management of skin rash is important, because data for both NSCLC and pancreatic cancers indicate that rash is associated with improved efficacy for erlotinib (see Table 1; see also Table 3 on page 561). The association between severity of rash and survival outcomes was analyzed in BR.21.[23] Median survival was significantly longer for those with grade 2+ rash. The median overall survival rates, by severity of rash, were 3.3 months (grade 0, n = 86), 7.1 months (grade 1, n = 135), and 11.1 months (grade 2+, n = 223).

The manufacturers and the FDA have added new safety information for erlotinib to the warnings and precautions sections of the prescribing information.[1,24] Gastrointestinal perforation (including fatalities); bullous, blistering, and exfoliative skin conditions (including cases suggestive of Stevens–Johnson syndrome/toxic epidermal necrolysis, in some cases fatal); and ocular disorders, including corneal perforation or ulceration, have been reported during erlotinib usage. This information was derived from routine pharmacovigilance activities of clinical study and postmarketing reports.[24]

Supporting Open-Label Studies

Two open-label studies have corroborated the results from study BR.21 (see Table 1). An expanded-access, phase 3b study in 229 patients with previously treated advanced NSCLC or those who were not candidates for chemotherapy reported that median overall survival was 6.3 months, with an overall response rate of 8.3%.[25]

TRUST, a phase 4 global, nonrandomized, open-label trial of erlotinib as a second-line or third-line therapy, plans to register more than 7,000 patients who had not responded to or who were unsuitable for chemotherapy, radiotherapy, or both. Early analysis showed an overall response rate of 12.6%, with a disease control rate of 68.8%.[20,26,27]

The median progression-free survival, calculated for 6,693 patients, was 3.2 months. No new safety signals were identified in this large population, and discontinuation rates resulting from an adverse event were similar to those observed in study BR.21 (5%).[20] These data are consistent with the positive findings from the phase 3 BR.21 trial and demonstrated that similar response and safety results were obtained in a nonselected population.

Comparison with Chemotherapy

Although results from trials directly comparing erlotinib and chemotherapy are not yet available, a historical comparison from individual studies suggests that erlotinib has efficacy similar to that of second-line chemotherapy while offering better tolerability. Phase 3 trials have reported a median overall survival of 8.3 months for pemetrexed (Alimta, Lilly) and 5.5 to 7.9 months for docetaxel (Taxotere, Sanofi-Aventis).[28–30] The median overall survival of 6.7 months with erlotinib from study BR.21 compares favorably with these data, considering the inclusion of patients with poor performance status (PS 3) and the use of erlotinib as third-line therapy in approximately 50% of the patients.[3] Furthermore, the disease control rate of 45% observed in the erlotinib trial is consistent with the rates of 42.7% and 55.2% for docetaxel and pemetrexed, respectively.

In patients who achieved a response, erlotinib appeared to offer a longer duration of response (7.9 months), compared with chemotherapy (4.6 months for pemetrexed and 5.3 to 9.1 months for docetaxel). Analysis of patients with a PS of 0 to 1 who received second-line treatment showed that median overall survival with erlotinib was comparable to chemotherapy (9.4 months vs. 9.1 months with docetaxel and 9.4 months with pemetrexed).[3,17,28]

An important distinction between erlotinib and second-line chemotherapy is the safety of these agents. Current cytotoxic agents used in the second-line setting are associated with severe hematological toxicity, and grade 3 or 4 neutropenia has been reported in more than 40% of patients receiving docetaxel.[28–30]

In a meta-analysis of 1,609 patients from 13 clinical studies, the rate of febrile neutropenia in patients receiving docetaxel was approximately 5.9%, and the use of prophylactic granulocyte-stimulating growth factors did not have a significant effect on the rate.[31] Febrile neutropenia can have an impact on quality of life both directly and indirectly, because it may lead to serious and potentially fatal infections. Further, it can result in interruption or reduction of treatment and may incur additional health care costs. In contrast, erlotinib monotherapy is generally not associated with life-threatening hematological toxicities.[3]

Erlotinib plus Chemotherapy for Untreated, Advanced Non–Small-Cell Lung Cancer

The use of erlotinib as a first-line therapy, in combination with chemotherapy, was tested in two randomized phase 3 studies, TALENT and TRIBUTE.[21,22] TRIBUTE, a phase 3 trial, evaluated the addition of erlotinib to carboplatin and paclitaxel (Paraplatin and Taxol, Bristol-Myers Squibb) as a first-line therapy for patients with advanced NSCLC who did not meet the primary endpoint of improving overall survival. TALENT (Tarceva Lung Cancer Investigation) was designed to evaluate cisplatin (Platinol, Bristol-Myers Squibb) and gemcitabine (Gemzar) with concurrent and continued erlotinib therapy compared with placebo.

These studies, in which patients received doublet chemotherapy with or without erlotinib, failed to show improved survival with erlotinib.[21,22] Similar results were observed in randomized studies utilizing gefitinib and chemotherapy.[32,33] However, a prespecified subset analysis of TRIBUTE found that never-smokers who received erlotinib experienced prolonged overall survival (median, 22.5 vs. 10.1 months with placebo; HR = 0.49).[21]

A retrospective subgroup analysis of the small number of never-smokers (18 of 1,172 patients) in TALENT (gemcitabine/cisplatin plus erlotinib or placebo) reported a median overall survival for patient never-smokers of 11.4 months with

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placebo (n = 10), and the median overall survival was not yet reached in the erlotinib group (n = 8).[22] The median progression-free survival rates were 7.9 months with erlotinib and 5.4 months with placebo (HR = 0.195).

The NCCN guidelines now recommend the use of erlotinib with or without chemotherapy as first-line treatment of advanced NSCLC in patients with a never-smoking history, in addition to those with known activating *EGFR* mutation or *EGFR* gene amplification.[34]

Potential for Patient Selection and Role of Biomarkers with *EGFR*–TKI Therapy

Erlotinib Studies

A retrospective analysis of tumor samples from a subset of patients treated with erlotinib in the BR.21 study reported that 38% (61 of 159 patients) were *EGFR* FISH-positive, 17% (34 of 204 patients) had *EGFR*-activating mutations, and 15% (30 of 206 patients) had *KRAS* mutations.[35] Correlation of this biomarker analysis with efficacy showed that response rates were significantly greater for patients with mutated *EGFR* (27% vs. 7% for wild-type *EGFR*; $P = 0.03$) and who were FISH-positive (21% vs. 5% for FISH-negative; $P = 0.02$). *EGFR* FISH positivity and wild-type *KRAS* status predicted a significant survival advantage with erlotinib (HR = 0.43, $P = 0.004$ and HR = 0.60, $P = 0.03$, respectively).[35]

The influence of FISH positivity and *EGFR* overexpression is being investigated in a prospective phase 2 trial of 143 patients randomly assigned to receive treatment with single-agent erlotinib or erlotinib plus carboplatin and paclitaxel.[36] The primary endpoint (progression-free survival rates at six months) was significantly higher in patients with *EGFR* mutations (89%) than in those with no mutations (23%) (HR = 0.17; $P = 0.003$). A subanalysis of *EGFR* mutations in a study of 291 patients showed that patients treated with erlotinib (n = 12) or gefitinib (n = 22) had a median overall survival of 20 months.[37]

Although these results support the NCCN's recommendation to use erlotinib as a first-line therapy in selected patients, there are currently no biomarkers that can be used to exclude patients from TKI therapy.[34] Additional studies are ongoing or planned to investigate the role of various biomarkers and response to erlotinib (see Discussion, page 560).

Supporting Studies

Several retrospective analyses have examined the effect of *EGFR* biomarker status on clinical outcomes in patient treated with gefitinib.[38–40] An analysis of *EGFR* mutation status from 83 Spanish patients reported improved median overall survival in patients with *EGFR* mutations (13 months), compared with those without mutations (4.9 months) ($P = 0.02$).[38]

A study of 102 patients showed improved median overall survival in those who were *EGFR* FISH-positive (18.7 months) compared with those who were FISH-negative (7 months) ($P = 0.03$).[39] Similarly, for 81 patients with bronchioloalveolar carcinoma subtypes, median overall survival and median progression-free survival rates were improved for FISH-positive patients (8 months vs. approaching 18 months, $P = 0.042$; 9 months vs. 4 months; $P = 0.072$, respectively).[40]

In a prospective examination of *EGFR* status and outcomes, the phase 3 Iressa Pan Asia Study (IPASS) study randomized 1,217 patients with untreated advanced NSCLC, and who were never-smokers or were former light smokers, to receive gefitinib or chemotherapy.[41] Progression-free survival was significantly prolonged in patients with *EGFR* mutations (n = 437) in the gefitinib arm, compared with those receiving chemotherapy (HR = 0.48; $P < 0.0001$). Conversely, in patients with *EGFR* mutation-negative NSCLC, chemotherapy afforded significantly better progression-free survival (HR, gefitinib vs. chemotherapy = 2.85; $P < 0.0001$).

Costs Associated with Erlotinib in Previously Treated, Advanced Non–Small-Cell Lung Cancer

Analyses of costs and cost benefits with erlotinib as second-line or third-line therapy for stage IIIB/IV NSCLC are favorable (Table 2).[42–44] The cost impact of erlotinib was modeled according to the perspective of a health insurer in the U.S. with 500,000 members in 2005.[42] Based on assumptions of the incidence of NSCLC and the use of erlotinib by line of therapy, the budget impact was estimated to be $0.01 per member per month.

A separate model, based on an indirect comparison of clinical trial data, evaluated the cost benefit of erlotinib compared with docetaxel or pemetrexed. A slight increase in quality-adjusted life-years was associated with erlotinib (0.42) compared with docetaxel (0.41) and pemetrexed (0.41), reflecting less severe complications of therapy and oral administration.[43] Again, erlotinib was associated with lower administration and adverse event costs that resulted in lower total costs compared with chemotherapy (see Table 2). A retrospective analysis of costs from payer claims submitted between 2002 and 2006 confirmed that erlotinib use resulted in the lowest costs, compared with docetaxel and pemetrexed, in both the second-line and third-line settings (see Table 2).[44]

PANCREATIC CANCER

Almost 42,500 new cases of pancreatic cancer were projected to be diagnosed in 2009.[7] Pancreatic cancer is the fourth leading cause of cancer-related deaths in males and females (35,240 deaths). Incidence and mortality rates are nearly identical for the U.S. and globally, highlighting the extremely poor prognosis for patients with this disease.[7,45] For all stages of pancreatic cancer, the one-year and five-year survival rates are 24% and 5%, respectively, and 98% of patients are expected to die as a result of this disease.[7,46] Even for patients with localized disease, the five-year survival rate is only 20%.

Progress in the management and early detection of pancreatic cancer has been slow. Because of inherent difficulties in early detection and a high risk of metastasis, only 7% of patients present with early-stage disease and few patients (15% to 20%) present with resectable disease, when surgery offers a chance for cure.[7,47]

Advanced Pancreatic Cancer

Since the mid-1990s, gemcitabine chemotherapy has been regarded as the standard of care for metastatic pancreatic cancer.[48] Randomized trials that include gemcitabine have reported median survival times between five and six months, with one-year survival rates below 20%.[49,50] The advent of

Table 2 **Cost Analyses of Erlotinib in Pancreatic Cancer and Non–Small-Cell Lung Cancer (NSCLC)**

Author/Study	Disease	Analysis	Results
Danese et al., 2008[53]	Pancreatic cancer	Budget–impact model	PMPM: $0.02
Ramsey, 2006[42]	2nd- or 3rd-line NSCLC	Budget–impact model	PMPM: $0.01
Carlson et al., 2008[43]	2nd- or 3rd-line NSCLC	Cost–benefit model	Total cost • Erlotinib: $37,000 • Docetaxel: $39,100 • Pemetrexed: $43,800
Ramsey et al., 2008[44]	2nd- and 3rd-line NSCLC	Cost analysis from patient claims	PPPM cost for 2nd-line use • Erlotinib: $2,929 • Docetaxel: $4,446 • Pemetrexed: $6,276 PPPM cost for 3rd-line use • Erlotinib: $3,256 • Docetaxel: $3,569 • Pemetrexed: $4,266

PMPM = per member per month; PPPM = per patient per month.

molecular targeted therapies has spurred investigation of these agents in this setting. To date, clinical trials conducted with these agents have not shown a meaningful survival benefit compared with gemcitabine monotherapy.[49] Erlotinib is the first targeted agent and the only *EGFR* inhibitor to significantly improve the survival of patients with untreated locally advanced or metastatic pancreatic cancer, when combined with gemcitabine, compared with gemcitabine alone.[4]

The efficacy of erlotinib was demonstrated in a randomized, double-blind, placebo-controlled phase 3 trial, study PA.3 (Table 3).[4] In this trial, 539 patients with untreated, advanced pancreatic cancer received erlotinib plus gemcitabine or placebo plus gemcitabine. Overall survival results revealed an HR of 0.82 (P = 0.038), representing an overall 22% relative improvement in survival or, alternatively, an 18% reduction in the risk of death.[4]

Median overall survival rates were 6.24 months for erlotinib plus gemcitabine and 5.91 months for chemotherapy alone.[4] Secondary efficacy measurements corroborated the benefit of treatment with erlotinib and gemcitabine. The one-year survival rate was greater with erlotinib plus gemcitabine (23% vs. 17%; P = 0.023) and progression-free survival was significantly longer (3.75 vs. 3.55 months), with an estimated HR of 0.77 (P = 0.004).[4] Further, at the approved prescribed dose for oral once-daily erlotinib at 100 mg, the disease control rate was higher than that for placebo (59% vs. 49.4%; P = 0.036).[4]

The combination of gemcitabine and erlotinib was well tolerated; grade 3 or 4 toxicities were similar, except for diarrhea and cutaneous rash, which were more frequent with the erlotinib and gemcitabine arm.[4] As previously noted with other *EGFR* inhibitors in colon cancer, there is a relationship between the grade of skin rash associated with *EGFR* therapy and the efficacy of erlotinib in pancreatic cancer.[51,52] Of the 282 patients who received erlotinib in the PA.3 trial, 79 had no rash, 102 had a grade 1 rash, and 101 had a grade 2 or higher skin rash.[4] Patients survived significantly longer if a skin rash developed (HR = 0.74; P = 0.037). The median survival rate with a grade 0 rash was 5.3 months; for a grade 1 rash, it was 5.8 months; and for a grade 2+ rash, it was 10.5 months. Corresponding one-year survival rates were 16% for a grade 0 rash, 9% for a grade 1 rash, and 43% for a grade 2+ rash (P = 0.001).

Predicted Costs Associated with Erlotinib

Danese et al. estimated the impact of the costs associated with the use of erlotinib for pancreatic cancer from a budget-impact cost model using a hypothetical health plan of 500,000 members.[53] The relatively low incidence of pancreatic cancer, combined with the assumption that only 23% of new patients would be treated with erlotinib plus gemcitabine and the short duration of treatment, suggested that the use of erlotinib in this setting would have a relatively low budgetary impact. Incremental costs associated with the addition of erlotinib to gemcitabine resulted in a budget impact of $0.02 per member per month; this estimate included the costs of administration and drug-related adverse events.

The most significant contributor to costs was duration of treatment. The model assumed a treatment duration of 15.7 weeks, based on data from clinical trial results. Although the cost effectiveness of erlotinib for pancreatic cancer has not been fully determined, the projected impact on the budget of health plans is minimal. The cost effectiveness for patients with a rash (grade 2 or greater) is likely to be more favorable because of the increased clinical benefit.

DISCUSSION AND FUTURE TRENDS

Patients with advanced NSCLC or pancreatic cancer are in urgent need of effective treatments that can prolong survival and improve quality of life. Erlotinib is the only targeted agent that significantly improves survival and offers symptom relief to patients with advanced NSCLC who have not responded to chemotherapy. Further, erlotinib is the first therapy in more than a decade and the first targeted agent to significantly

improve survival in patients with advanced pancreatic cancer. Taken together, the comparable efficacy of erlotinib to chemotherapy, combined with the more tolerable safety profile and the convenience of oral administration, position erlotinib as preferred single-agent therapy for second-line and third-line treatment of patients with advanced NSCLC. Erlotinib is more cost-effective than chemotherapy for NSCLC, and the overall cost impact on health insurers is acceptable for both NSCLC and pancreatic cancer.

Erlotinib continues to undergo vigorous clinical investigation to optimize its use in treating NSCLC, both as single-agent therapy and in combination with chemotherapy, and to identify patients who will derive optimal benefit (Table 4). SATURN (Sequential Tarceva in Unresectable NSCLC), a trial that evaluated erlotinib as maintenance therapy, following first-line chemotherapy for advanced disease in responding patients, achieved the primary endpoint of prolonged progression-free survival.[54] The aim of the randomized phase 3 trial called TORCH (Tarceva or Chemotherapy for the Treatment of Advanced NSCLC) is the most appropriate and cost-effective sequential approach for erlotinib and chemotherapy in an unselected population of patients with metastatic NSCLC.[55] In this trial, the relationship between biomarkers (*EGFR* and *KRAS* mutational status) and treatment response to erlotinib will be able to be evaluated. Both SATURN and TORCH are expected to provide early insight into how to combine erlotinib with first-line chemotherapy.

The failure of the first-line combination trials was postulated to be a result of *EGFR*–TKIs being antagonistic with chemotherapy by arresting the cell cycle; however, the sequential administration of erlotinib and chemotherapy might be superior to chemotherapy alone.[56,57] The phase 2 FAST–ACT trial (First-Line Asian Sequential Tarceva plus Chemotherapy Trial) examined an alternative treatment sequence; 154 patients (94% Asian) received a gemcitabine-platinum doublet for a maximum of six weeks with subsequent randomization to erlotinib or placebo, combined with chemotherapy, on days 15 and 28 of each four-week chemotherapy cycle.[58] The responding patients continued to receive erlotinib or placebo until disease progression. The median progression-free survival was significantly improved in the erlotinib arm (7.2 vs. 5.5 months, HR = 0.57; $P = 0.02$). It may be that novel dosing schemes, as used in FAST–ACT, might be required.

Moving toward identifying appropriate patients for first-line treatment, the randomized French trial IFCT–GFPC 05.02 is designed to assess maintenance therapy with erlotinib after first-line chemotherapy in patients with good performance status (PS 0–1) (see Table 4).

The Spanish Lung Cancer Group plans to evaluate the benefit of first-line erlotinib compared with chemotherapy in patients with *EGFR* mutations in the phase 3 EURTAC trial (European Tarceva versus Chemotherapy).[55] Additional phase 2 trials by the Cancer and Leukemia Group B and other teams will evaluate erlotinib with chemotherapy according to patient predictors such as smoking history.[55]

In the second-line advanced NSCLC setting, two phase 3 trials are investigating whether biomarkers can be used to target therapy to patients (se Table 4). Biomarkers will be assessed in patients enrolling in the TITAN study (Tarceva in Treatment of Advanced NSCLC), which compares erlotinib with pemetrexed or docetaxel.[17] MARVEL (Marker Validation for Erlotinib in Lung Cancer), a phase 3 trial, is being conducted to evaluate outcomes in approximately 1,200 patients, based on *EGFR* FISH status and who receive erlotinib or pemetrexed.[59] Secondary analyses in this study will be conducted by *EGFR* expression and mutation status. Both TITAN and MARVEL should afford decision makers, payers and health care professionals the opportunity to compare the effectiveness of erlotinib with chemotherapy.

Erlotinib is also being investigated in combination with

Table 3 Efficacy of Erlotinib as a First-Line Therapy for Advanced Pancreatic Cancer

	Erlotinib + Gemcitabine (n = 285)	Placebo + Gemcitabine (n = 284)	Hazard Ratio and/or *P* Value
Median survival	6.24 months	5.91 months	HR = 0.82; $P = 0.038$
1-year survival	23%	17%	$P = 0.023$
Median PFS	3.75 months	3.55 months	HR = 0.77; $P = 0.004$
DCR	59%	49.4%	$P = 0.036$
Analysis of survival by grade of skin rash			
Median survival Grade 0 Grade 1 Grade 2+	 5.3 months 5.8 months 10.5 months	N/A	$P = 0.037$
1-year survival Grade 0 Grade 1 Grade 2+	 16% 9% 43%	N/A	$P < 0.001$

DCR = disease control rate (complete response + partial response + stable disease); N/A = not available; PFS = progression-free survival.

Table 4 Key Ongoing and Planned Erlotinib Trials in Non–Small-Cell Lung Cancer (NSCLC)

Study	Setting
Adjuvant	
RADIANT	Adjuvant use in patients with *EGFR* FISH-positive or IHC-positive status
First-line advanced	
SATURN	Maintenance use
IFCT–GFPC 05.02	Maintenance use in patients with PS 0–1
TORCH	Sequential erlotinib plus chemotherapy
Spanish Lung Cancer Group	Use in patients with *EGFR* mutations
Second-line advanced	
TITAN	Biomarker assessment with second-line erlotinib vs. chemotherapy
MARVEL	Biomarker assessment with second-line erlotinib vs. pemetrexed
Combination use	
ATLAS	Maintenance use (bevacizumab plus erlotinib) in first-line advanced NSCLC

EGFR = epidermal growth factor receptor; FISH = fluorescence *in situ* hybridization; IHC = immunohistochemistry; PS = performance status.
Trials: ATLAS = A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Trial Comparing Bevacizumab Therapy with or without Erlotinib after Completion of Chemotherapy with Bevacizumab for the First-Line Treatment of Locally Advanced, Recurrent, or Metastatic NSCLC; IFCT–GFPC = A Randomized phase 3 Trial Assessing in Patients with Advanced NSCLC Not Progressing on First-Line Cisplatin–Gemcitabine Chemotherapy Maintenance Chemotherapy with Gemcitabine or Sequential Treatment with Erlotinib; MARVEL = Marker Validation for Erlotinib in Lung Cancer; RADIANT = A Study of Tarceva after Surgery with or without Adjuvant Chemotherapy in NSCLC Patients Who Have EGFR-Positive Tumors (Adjuvant); SATURN = Sequential Tarceva in Unresectable NSCLC; TITAN = Tarceva in Treatment of Advanced NSCLC; TORCH = Tarceva or Chemotherapy for the Treatment of Advanced NSCLC.

other targeted agents. The clinical success of both erlotinib and bevacizumab (Avastin, Genentech) as a therapy for NSCLC provides a rationale for evaluating this combination. The Beta/Tarceva trial (BeTa), which compared bevacizumab plus erlotinib with erlotinib alone in second-line therapy (patients who had failed to respond to one line of chemotherapy), showed no difference in survival for patients with previously treated NSCLC.[60]

The randomized phase 3 ATLAS trial enrolled 1,160 patients to evaluate the combination of bevacizumab and erlotinib as maintenance therapy following initial treatment with bevacizumab plus chemotherapy (see Table 4).[61] A preplanned interim analysis showed that the combination of the two drugs as maintenance therapy significantly extended progression-free survival in patients responding to initial treatment.[61] The trial was stopped early because of the positive results. Erlotinib as maintenance therapy is also being investigated in the adjuvant setting.

RADIANT, a phase 3 trial (see Table 4), is expected to test erlotinib as a maintenance therapy following surgery and chemotherapy (if used) in patients with *EGFR*-positive, early-stage NSCLC, as determined by FISH or IHC analysis.[55]

Likewise, the clinical success of erlotinib has spurred further clinical investigation in pancreatic cancer (Table 5). The almost doubling of the one-year survival rate in patients with a grade 2+ skin rash has provided the impetus for several studies. A large phase 2 trial is expected to investigate the dose escalation of erlotinib, in combination with gemcitabine, to the development of skin rash and the effect on clinical outcomes.[55] A second phase 2 study is evaluating the correlation between skin rash and the prescribed 100-mg once-daily dose of erlotinib, with chemotherapy, in the metastatic setting.[55]

Erlotinib is also being studied with other chemotherapies and treatment modalities. Phase 1 results from 18 evaluable patients with locally advanced pancreatic cancer, treated with erlotinib plus gemcitabine and radiation, showed a median survival of 18.7 months, and treatment was well tolerated.[62] Erlotinib is under investigation in relapsed pancreatic cancer, for which even fewer treatment options exist and few clinical studies have been conducted.

In a phase 2 trial, 30 patients with gemcitabine-refractory metastatic disease who had not received anti-*EGFR* therapy received erlotinib and capecitabine.[63] The combination had

Table 5 Future Directions for the Study Of Erlotinib in Pancreatic Cancer

- Correlation between skin rash and the prescribed 100-mg dose
- Dose escalation to the development of skin rash
- Treatment of relapsed advanced disease
- Patient selection according to biomarkers
- Treatment of locally advanced pancreatic cancer
- Treatment of early-stage pancreatic cancer

activity, and the median survival was 6.5 months.

Although erlotinib's potential to exert its greatest benefit in early-stage pancreatic cancer warrants further research, the difficulty of detecting early-stage disease may hinder clinical investigation. As with its use in NSCLC, the benefit of erlotinib may be further enhanced by selecting patients with pancreatic cancer who are likely to respond to this therapy. Several potential predictive markers (*EGFR*-activating mutations, *EGFR* amplification) have been identified, but their value remains to be confirmed in clinical trials.

CONCLUSION

The results of many planned studies are eagerly anticipated and will build upon the survival and patient benefits derived from erlotinib by determining the most effective uses in combination with chemotherapy, the optimal settings for intervention, and the patients who derive the greatest benefit. To make progress in treating these challenging diseases will require options that prolong survival and improve quality of life.

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